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Risk factors for late kidney allograft failure

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Risk factors for late kidney allograft failure.

Background. While graft survival rates in the short term have improved dramatically, only a modest improvement has been shown in long-term graft survival rates. We evaluated the causes of late failure in renal allograft recipients treated with cyclosporine A (CsA).

Methods. A total of 864 adults with a functioning graft at one year were evaluated. The end points were dialysis or death with a functioning graft.

Results. The 13-year patient and graft survival probabilities were 0.82 and 0.64, respectively. The graft half-life was 20.1 years and the pure graft half-life was 31.1 years. At multivariate analysis, plasma creatinine at one year ($P = 0.0006$; RR 1.72), low-density lipoproteins (LDL) at one year ($P = 0.0014$; RR 1.65), older age ($P = 0.0128$; RR 1.50) and delayed graft function ($P = 0.0350$; RR 1.45) were associated with the end point. Chronic allograft nephropathy was the cause of failure in 97 patients, death in 70, recurrence of glomerulonephritis in 24, other events in 6. Cardiovascular complications were the most frequent cause of death. Post-transplant cardiovascular events were associated with: pre-transplant cardiovascular events ($P = 0.0012$; RR 2.65), older age ($P = 0.0001$; RR 2.46), pre-transplant arterial hypertension ($P = 0.0249$; RR 1.57), smoking ($P = 0.0235$; RR 1.29), duration of dialysis ($P = 0.0229$; RR 1.28). Mean serum cholesterol, LDL and triglycerides were each significantly associated post-transplant cardiovascular events.

Conclusions. The graft half-life was 20 years. Chronic allograft nephropathy was the leading cause of late failure, followed by death. If the data were censored by death, the projected pure graft half-life would be 31.1 years. Pre-transplant selection and preparation of the candidate as well as appropriate life style are recommended to improve life expectancy and extend graft survival.

With the modern immunosuppression the risk of early graft failure has been considerably reduced. Today, the one-year cadaveric allograft survival probability is around 90% in many transplant units. However, despite the remarkable improvement of graft survival in the short-term, large surveys reported only a modest increase in the projected graft half-life [1]. Therefore, the attention of the transplant community is now focused on the causes of late allograft failure and their prevention.

In this retrospective analysis of a single-center experience, we tried to identify the risk factors associated with late failure in renal transplant recipients who were treated with cyclosporine (CsA) and who had their kidney allograft functioning for at least one year.

Key words: kidney transplantation, chronic allograft nephropathy, mortality in renal transplantation, glomerulonephritis, immunosuppression, life style post-transplantation.

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METHODS

Criteria for inclusion

The following inclusion criteria were followed for enrolling patients into the analysis: (*a*) age more than 15 years at transplantation; (*b*) first renal transplantation; (*c*) treatment with CsA since transplantation; (*d*) an allograft functioning for at least one year.

Five patients who received double organ transplants and 12 who stopped CsA before the first year were excluded from this analysis.

Definitions

For the aims of this study, chronic allograft nephropathy was defined as a progressive decline of graft function not related to treatment interruption, recurrence of original disease, vascular or urological complications. No attempt to differentiate chronic renal toxicity from chronic rejection was made.

Recurrence of glomerulonephritis was always diagnosed by transplant biopsy. All patients with diagnosis of recurrence had a histological diagnosis of the original disease on their native kidneys. Graft loss was attributed to recurrence both on clinical grounds (nephrotic proteinuria, micro- or macroscopic hematuria) and graft biopsy features showing for any subtype of glomerulonephritis the typical pattern on immunofluorescence and the characteristic glomerular lesions often associated with diffuse glomerular sclerosis or with crescents, particularly in proliferative nephritis such as IgA nephritis, Henoch-Schönlein disease and membranoproliferative glomerulonephritis.

Table 1. Mean demographic characteristics of 864 patients at transplantation

Age *median (min–max)*	39.8 years (15–69)
Sex *male/female*	567/297
Living/cadaver donor	151/713
Duration of dialysis *median*	28 months (0–270)
Chronic glomerulonephritis	374
Polycystic kidney disease	90
Urological disease	78
Congenital disease	63
Systemic disease	46
Miscellaneous	66
Undetermined	147

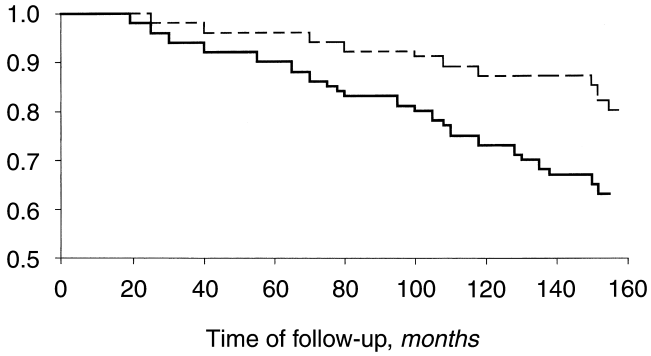

Fig. 1. Patient (dashed line) and graft (solid line) survival probabilities in 864 cyclosporine A (CsA)-treated renal transplant recipients with their graft functioning at one year.

These glomerular lesions were often associated with vascular and tubulointerstitial lesions.

Delayed graft function was defined as the need of one or more dialysis sessions after transplantation.

More difficult was the definition of smokers. We included in the same group the ex-smokers and those patients who were smoking continuously at least five cigarettes per day, while non-smokers were considered to be patients who never smoked or smoked only sporadically.

Statistical analysis

Cumulative probability of graft survival and of recurrence of glomerulonephritis was estimated according to Kaplan and Meier [2]. The prognostic relevance of baseline covariates for univariate and multivariate analyses was assessed by means of the stratified Cox models. The role of prognostic factors has been assessed for the following variables at transplantation: sex, age (>45 vs. ≤45 years), source of donor, type of dialysis, months on dialysis (>60 vs. ≤60 months), pre-transplant hypertension (need for one or more drugs), smoking (continuing, any amount), body mass index (>25 vs. ≤ 25 wt/ht^2), hepatitis B and C virus (HBV, HCV) status, number of human lymphocyte antigen (HLA) mismatches, and left ventricular hypertrophy. After transplantation the following variables have been considered: type of immunosuppression (CsA alone vs. CsA plus steroids vs. CsA plus steroids plus azathioprine or mofetil mycophenolate or sirolimus/everolimus), number of acute rejections (within the first three months), number of high-dose methylprednisolone pulses, use of antilymphocyte antibodies, delayed graft function, plasma creatinine (>1.5 vs. ≤1.5 mg/dL), hypertension [mean arterial pressure (MAP) <110 mm Hg vs. either MAP <110 mm Hg under treatment or >110 mm Hg], hematocrit (>36 vs. <36%), serum cholesterol (>250 vs. <250 mg/dL), serum low-density lipoproteins (LDL; >160 vs. <160 mg/dL), serum triglycerides (>160 vs. <160 mg/dL) at one year. These thresholds have been chosen according to their clinical relevance.

The end points for graft failures were need of regular dialysis or death with functioning graft.

Pure patient and graft survivals were calculated by censoring the data by death. Graft half-life was calculated according to the method of Cho and Terasaki [3].

The prognostic impact on cardiovascular events has been evaluated considering also the role of lipid metabolism variables (serum cholesterol, triglycerides, HDL, LDL), blood pressure, smoking and hematocrit, recorded at transplantation, after six months, and then yearly. Since the cardiovascular events occurred with a maximal incidence in the first three post-transplant years, we followed a pragmatic approach by fitting three models, trying to evaluate the prognostic relevance of the pattern of these time-dependent variables at three different times since transplantation. For the first model, the variables taken into account were those recorded at baseline; the mean of the values recorded at the sixth month and at one year has been included in the second model and, finally, the mean of the values recorded in the first three years in a third model.

RESULTS

Eight hundred sixty-four renal transplant patients, who received their allografts between February 1983 and June 2000, met the criteria for inclusion and were enrolled in this study. The demographic characteristics are given in Table 1. The patient survival probability at 13 years was 0.82, the graft survival probability at 13 years was 0.64 (Fig. 1).

Risk factors for graft failure

The mean graft half-life was 20.1 years, 18.7 for cadaveric transplants and 31.9 for living transplants. The most frequent cause of late failure was chronic allograft nephropathy (97 of 197 events, 49.2%), followed by death (70 events, 35.5%), recurrent glomerulonephritis (24 events, 12%), renal vessel thrombosis (3 cases, 1.5%), graft malignancy (2 cases, 1.0%), and urological complication (1 case, 0.5%). Univariate analysis showed that plasma

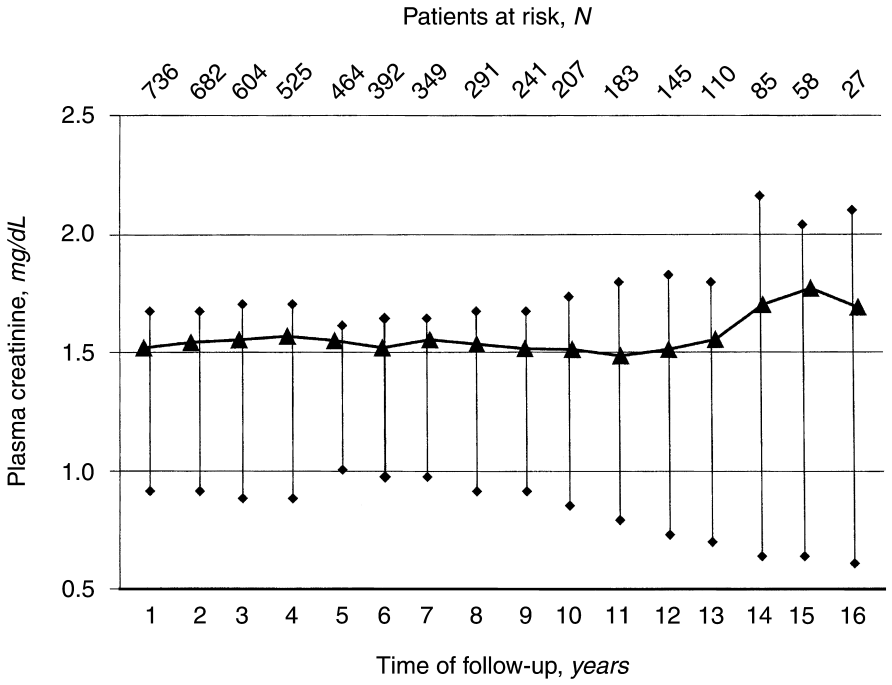

Fig. 2. Mean plasma creatinine levels (mg/dL; ▲) and standard deviation (±; ◆) in patients with their graft still functioning.

creatinine >1.5 mg/dL at one year ($P = 0.0001$), delayed graft function ($P = 0.0003$), age older than 45 years ($P = 0.0015$), duration of dialysis longer than 60 months ($P = 0.0028$), and serum LDL more than 160 mg/dL at one year ($P = 0.0065$) were significantly associated with late failure.

At multivariate analysis, increased plasma creatinine ($P = 0.0006$; RR 1.72), elevated LDL ($P = 0.0014$; RR 1.65), older age ($P = 0.0128$; RR 1.50) and delayed graft function ($P = 0.0350$; RR 1.45) were significantly associated with late failure.

Chronic allograft nephropathy

Loss of graft caused by chronic allograft nephropathy occurred in 97 of 864 patients (11.2%). Graft failure occurred in mean after 85.0 ± 47.3 months (median 80.8 months; range 12 to 203).

The mean reciprocal of plasma creatinine tended to maintain stable until 13 years in patients with their allografts still functioning (Fig. 2).

To evaluate whether graft survival probabilities changed over the years, two different time periods were compared. The ten-year graft survival probability was significantly better for patients transplanted between 1989 and 1994 than for patients transplanted before 1983 and 1988 (Fig. 3).

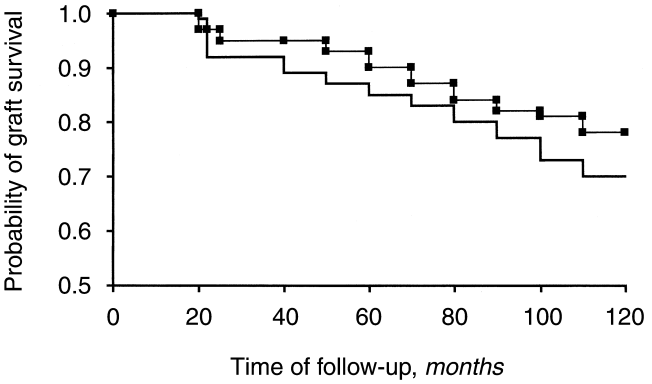

Fig. 3. Graft survival probability in two different periods (log-rank $P = 0.04$): (■) 1989 to 1994 and (solid line) 1983 to 1988.

Death

Death occurred in 70 patients, in mean 6.2 ± 3.79 years after transplantation, and was the second cause of late failure. In 24 cases death was caused by cardiovascular complications, in 19 by cancer, in 11 by infections, in 9 by liver disease and in 7 by miscellaneous causes.

The fatal cardiovascular complications were: myocardial infarction, 17 cases; cerebral hemorrhage, three; cardiac arrest, two; complicated aortic aneurysm, one; pulmonary edema, one. Death caused by cardiovascular events occurred in mean 91.4 ± 50.92 months after transplantation (median 79.13 months; range 13 to 175).

Among fatal cancers, four were lymphomas, four carcinomas of gastrointestinal tract, three lung cancers, two liver carcinomas, two pancreas carcinomas, two carcinomas of the native kidneys, one carcinoma of the transplanted kidney, and one Kaposi sarcoma. Death caused by cancer occurred in mean 81.9 ± 55.95 months after transplantation (median 69.6 months; range 17 to 185).

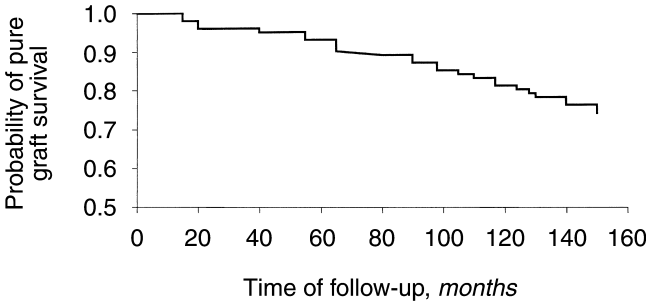

Fig. 4. Pure graft survival probability, excluding death.

Pneumonia ($N = 2$), post-surgical sepsis, in patients with polycystic kidney disease (2), necrotizing colitis with sepsis (1), cholangitis (1), disseminated tuberculosis (1), AIDS (1), sepsis of unknown origin (1), urinary sepsis and cachexia in a patient with polycystic kidney disease (1), and intestinal perforation and sepsis (1) were the causes of death from infection.

Death due to liver failure occurred in four HBV positive patients, in two HBV and HCV positive patients, in one HCV positive patient. Two other patients were HBV negative while their HCV status was unknown (both patients died before 1989).

The pure graft survival was calculated by censoring the data for death. The 13-year pure graft survival without death was 0.72 (Fig. 4). The pure graft half-life was 31.1 years.

No attempt was made to search for risk factors of death caused by tumors or infections, due to the small number of events.

Risk factors for cardiovascular events

To analyze the risk factors associated with cardiovascular complications, since the number of fatal cardiovascular complications was too small to allow a sensible statistical analysis, we considered both the fatal and nonfatal first cardiovascular events that developed after transplantation. In a total of 154 cardiovascular events there were 44 severe cardiac arrhythmias, 38 occlusive peripheral arteriopathies, 32 cardiac infarctions, 19 angina pectoris, 16 cerebrovascular complications, five congestive heart failures, and two aortic aneurysms requiring surgery.

As shown in Table 2, among the pre-transplant variables, the risk of de novo cardiovascular events during the first year after transplantation was significantly associated with pre-existing cardiovascular events ($P = 0.0012$; RR 2.65), older age ($P < 0.0001$; RR 2.46), pre-transplant arterial hypertension ($P = 0.0249$; RR 1.57), smoking ($P = 0.0235$; RR 1.29), duration of dialysis ($P = 0.0229$; RR 1.28), and with the type of donor at a borderline significance level, while the lipid levels did not show any significant prognostic role. Then, considering the models fitted in the follow-up (after one and three years since transplantation), the type of donor remained at a borderline level or even less, pre-existing cardiovascular events lost their relevance, and pre-transplant arterial hypertension with duration of dialysis remained significant prognostic factors only until three years after transplantation (Table 2). Finally, elevated serum cholesterol, or serum LDL cholesterol or serum triglycerides only, added once at a time to the final model, gained an independent prognostic role, giving very similar increases of the relative risk for each 10 unit increase. If these three variables were jointly considered in a prognostic model, serum triglycerides remained into the model as an independent prognostic factor.

Recurrence of glomerulonephritis

Recurrent glomerulonephritis accounted for 24 graft failures. Failure occurred in a mean 74.8 ± 51.34 months (median 61.6 months, range 12 to 171). In 12 cases the cause was IgA nephritis, in four cases it was membranoproliferative glomerulonephritis, in three cases membranous nephropathy, in three cases focal and segmental glomerulosclerosis, and in two the cause was Henoch-Schönlein nephritis.

The 13-year graft survival probabilities were the same in patients transplanted because of a primary glomerulonephritis and in patients transplanted because of other diseases (Fig. 5).

DISCUSSION

In this retrospective single-center analysis, we chose a hard endpoint, namely the need for regular dialysis or death with a functioning allograft. Among a large number of variables taken into consideration, only elevated plasma creatinine at one year, elevated LDL at one year, older age of the recipient, and delayed graft function were significantly associated with late graft failure at multivariate analysis. On the contrary, no effect of HLA matching was observed. This may be accounted for partly by the fact that more than 80% of our patients had two to four HLA incompatibilities, which precluded the ability to judge the impact of an excellent or a very poor compatibility. On the other hand, the number of patients in this study was too small to allow significant differences between the various grades of mismatch to be found. Reports showing a statistically significant impact of HLA on graft outcome were based on national or international surveys including many thousands of renal allografts [4, 5].

Previous studies already pointed out that graft function at 12 months is a strong surrogate marker of late graft outcome [6, 7]. Hyperlipidemia is not only a well established risk factor for cardiovascular complications, but also can be responsible of graft vascular lesions eventually leading to progressive chronic allograft nephropa-

Table 2. Multivariate analysis of risk factors for cardiovascular events following transplantation

	Prognostic models								
	Model 1[a]			Model 2[b]			Model 3[c]		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Age at transplantation									
>45 vs. <45 years	2.46	1.744–3.466	0.0001	2.46	1.662–3.631	0.0001	2.33	1.483–3.673	0.0003
Living vs. cadaveric donor	0.55	0.304–1.012	0.0548			0.2846	0.46	0.197–1.053	0.0659
Smoking *yes vs. no*	1.29	1.035–1.611	0.0235	1.32	1.018–1.707	0.0360	1.42	1.049–1.921	0.0233
Months on dialysis									
>60 vs. <60	1.28	1.035–1.587	0.0229	1.42	1.119–1.813	0.0041			0.3456
Cardiovascular disease before transplant *yes vs. no*	2.65	1.472–4.787	0.0012			0.1589			0.1834
Pre-transplant hypertension	1.57	1.059–2.328	0.0249	1.63	1.045–2.556	0.0314			0.1088
And									
Triglycerides[d]			0.4663	1.02	1.002–1.040	0.0318	1.03	1.009–1.048	0.0038
Or									
Total cholesterol[d]			0.9404	1.06	1.020–1.091	0.0018	1.06	1.020–1.110	0.0040
Or									
LDL cholesterol[d]			0.3077	1.06	1.014–1.103	0.0098	1.08	1.019–1.145	0.0091

[a] Model 1: For the 1st year post-transplant, considering triglycerides, total cholesterol and LDL cholesterol basal values
[b] Model 2: For the 2nd and 3rd year post-transplant, triglycerides, total cholesterol and LDL cholesterol (mean of the 6th month and 1st year values)
[c] Model 3: For follow-up after the 3rd year post-transplant, triglycerides, total cholesterol and LDL cholesterol considered are the mean of 1st, 2nd, and 3rd year values
[d] RR per each 10 mg/dL value increase of these variables

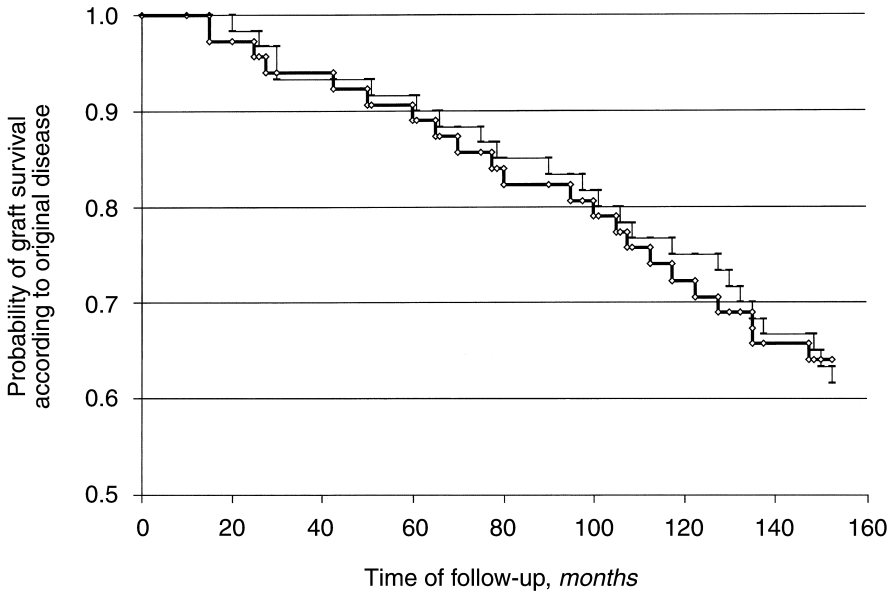

Fig. 5. Graft survival probability in 374 renal transplant recipients with glomerulonephritis as a primary cause of renal failure (◇) and in 490 patients with other causes of renal failure (-).

thy [8, 9]. There is a general agreement that an older age of the recipient may expose the patient to an increased risk of mortality and morbidity. Moreover, the morbid events that occur more frequently in older patients may require a reduction of immunosuppressive therapy with consequent increased risk of late irreversible rejection [10]. Whether delayed graft function is [11, 12] or is not [13, 14] independently associated with an increased rate of graft function is still under discussion. In this study delayed graft function emerged as an independent variable that increased the risk of late failure by 45%. Clearly, however, it is likely that all of these variables remaining in the multivariate model can act in concert to cause late graft failures.

Chronic allograft nephropathy was the most frequent cause of graft failure in this study as well as in most other analyses and surveys. However, only 11% of our patients eventually lost their allograft because of chronic allograft nephropathy and this occurred in mean after 85 months. Consequently, the graft half-life was good, ranging around 19 years for cadaveric transplant recipients. For many years the data of the United Network for

Organ Sharing (UNOS) showed that, despite a dramatic reduction in the incidence of acute rejection after the introduction of CsA, the cadaveric graft half-life remained fairly stable, ranging around seven to eight years [15]. However, more recently the same source [1] and another large American survey [16] reported a progressive improvement of graft half-life in renal transplant recipients. These data are confirmed by our experience, as the long-term graft survival was significantly better in patients transplanted between 1989 and 1994 than in patients transplanted between 1983 and 1988. Several reasons may account for the improved results in the more recent period. These include better general medical care, the availability of newer antiviral and antimicrobial agents, and a better treatment of comorbidity. It is likely that the use of newer immunosuppressive drugs also contributed to a better graft survival, although no single regimen appeared to be statistically superior. The lack of difference between monotherapy, dual therapy and triple therapy with CsA was somewhat expected, as a recent multicenter trial showed a similar graft survival at 10 years in patients assigned to any of these three regimens [17]. Because of the good graft survival the number of patients assigned to mycophenolate mofetil or sirolimus/everolimus was too small to detect any significant difference. Of interest, in our patients, all of whom were treated with CsA, the mean plasma creatinine levels tended to remain stable over the time, confirming previous results showing that prolonged exposure to CsA does not necessarily lead to progressive graft dysfunction [18, 19].

Death with a functioning graft was the second cause of late failure in this series. As already pointed out by the UNOS results [15], our experience showed cardiovascular disease as the leading cause of death. Both pre-transplant and post-transplant variables influenced the risk of cardiovascular events. In agreement with other studies we found that pre-transplant variables such as previous cardiovascular events [20], age [20], arterial hypertension [20, 21] smoking [20, 22] and long-term dialysis [8, 23] significantly increased the risk of de novo cardiovascular complications after transplantation.

Diabetes is another well-recognized risk factor for cardiovascular disease, but since we transplanted very few diabetic patients, it did not emerge as a significant risk factor in our study. These data outline the importance of careful selection and preparation of the recipient before transplantation in order to prevent post-transplant cardiovascular complications.

After transplantation, the same variables plus hyperlipidemia increased the risk of cardiovascular complications. While age and duration of dialysis cannot be modified, these data emphasize that in transplant recipients, as well as in the general population, the lifestyle and the type of diet can influence the development of cardiovascular events. As cardiovascular disease may develop approximately 20 years earlier in renal transplant recipients than in general population [24], preventive measures such as aggressive treatment of hyperlipidemia, hypertension and diabetes are strongly recommended. Moreover, any effort should be done to convince the patients to avoid cigarette smoking, physical inactivity and excess weight.

Tumors were the second cause of death in this series. It is well known that transplant recipients are exposed to an increased risk of malignancy [25]. De novo malignancy is now emerging as a major cause of morbidity and late failure in renal transplantation [26]. Apart from age and genetic predisposition, the intensity and the duration of immunosuppression, the use of antilymphocyte antibodies, sun exposure and viral infections can favor the development of tumors in organ transplant recipients. Measures to reduce the risk of tumor may include low exposure to sun, avoidance of smoking, and low-dose immunosuppression whenever possible [27]. Regular surveillance is recommended in order to allow an early diagnosis of malignancy.

Infection is becoming more rare as a cause of death [12] and this was confirmed in this study. Progress in the diagnosis and treatment of infections as well as improved methods of immunosuppression certainly contributed to a consistent decline in the incidence of fatal infections.

Liver failure was the fourth cause of death and mostly occurred in HBV or HCV positive patients. HBV-positive renal transplant recipients may remain asymptomatic for years, but in the long-term they have an increased risk of death from liver cirrhosis and/or extrahepatic sepsis [28]. The prognosis seems to be better for HCV positive patients who have a life expectancy similar to that of HCV negative patients [29]. Nevertheless, a number of patients may develop liver cirrhosis and die, usually after 10 or more years. We did not take particular measures in HCV positive patients. We excluded from transplantation those patients with biopsy-proved chronic active hepatitis and tried to reduce immunosuppression when possible. Only three out of 126 HCV positive patients died from liver failure but two of them were also HBV positive. Two other HCV positive patients died from extra-hepatic infection, four from cardiovascular disease and three from extra-hepatic neoplasia. These data confirm that mortality is directly caused by liver failure only in a minority of HCV positive patients [30]. Whatever the cause of death, it is clear that mortality with graft functioning is a major limit for long-term graft survival. This is outlined by the increase of graft half-life from 20 to 30 years, after censoring our data by death.

Recurrent glomerulonephritis was the third cause of late failure. Previous studies pointed out that the graft loss was more frequent in patients with recurrent renal disease than in those without recurrence [31]. However, little attention has been paid to whether patients with glo-

merulonephritis have an increased risk of graft failure when compared with patients transplanted because of other diseases. In a previous study we found that the 10-year graft survival rate was similar in 106 patients transplanted because of IgA nephritis and in 212 controls, nor was there a difference in the 10-year graft survival between the patients with IgA nephritis with recurrence and those without recurrence [32]. As well, our study found no significant difference in the 13-year graft survival rate between patients with glomerulonephritis and those with other renal diseases. These data suggest that little impact of recurrent glomerulonephritis on graft survival exists at least until 10 to 13 years. However, it is possible or even likely that in the very long term, recurrence of glomerulonephritis may represent a major cause of kidney graft failure.

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